REMARKS

A. The Invention

The present invention concerns peptide sequence supermotifs characteristic of peptides that bind more than one HLA molecule. Using these novel supermotifs, antigens can be screened to identify peptides that bind more than one MHC allele and are capable of inducing a CTL response against the antigen. In particular, certain peptides are disclosed and claimed which manifest binding to a number of HLA alleles.

B. Amendment to the Specification

The Specification is amended to specifically recite a peptide having the sequence MPLETQLAI (SEQ ID NO:30). This peptide is disclosed at the second line of Table 12 of parental application U.S. Serial No. 08/344,824, which was incorporated by reference into the instant application at page 1, line 9. Thus, the amendment of the present Specification does not introduce new matter.

C. The Restriction

In paper 10 the Examiner imposed a 20-way restriction requirement on the 3 claims then pending in the present application.

Applicants traversed the restriction, but it was maintained. After a telephone February 20, 1998 telephone consultation with PTO biotechnology specialist Dr. Margaret Parr and the Examiner as well, it was agreed that the restriction does not comport with Patent Office practice, and that it should be withdrawn. Accordingly, Applicants understand from this conversation that all claims are to be examined in this application.

D. Status of the claims and pending rejections

Claims 1-3 were pending and claims 1-2 and 4-15 are pending upon entry of the present amendment .

Claims 1-3 were rejected under 35 U.S.C. § 112 (second paragraph) on the grounds that the claims were indefinite with regard to the following:

- metes and bounds of the word "peptide";

- meaning of the term "immunogenic peptide";
- meaning of the word "composition";
- meaning of the word "about";
- the term "therapeutically effective dose" allegedly does not make clear what kind of therapy is referred to;
- meaning of the term "HLA molecule".

Claims 1-3 were rejected under 35 U.S.C. § 112 (first paragraph) on the basis that the following are not enabled:

- over one billion peptides are encompassed by the claims;
- which epitopes are needed for inducing a CTL response;
- which peptides would retain functional activity;
- the peptide may be inactivated before producing an effect;
- the peptide may not reach the target area;
- the peptide may have adverse side effects.

Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Bosisio *et al.*, *Gazz. Chim. Ital.* 97(12)1848-57 (1967) or Fujii *et al.*, *Chem. Pharm. Bull.* 31(12)4259-4262 (1983). Bosisio *et al.*, see abstract, teach the peptide DPNKFIGLM. Fujii *et al.*, page 4261 (middle of page) teach the KPDQFVGLM peptide.

E. Response to the rejections

The claims are amended without prejudice to further prosecution. Applicants submit that the pending claims as amended are fully enabled by and described in the specification.

1. The terms "peptide", "immunogenic peptide", "composition", "about", "therapeutically effective dose" and "HLA molecule" are definite

a. "Peptide", "immunogenic peptide", "about", "therapeutically effective dose" and "HLA molecule" are definite

The rejections regarding these terms are rendered moot in view of the amendments to the claims. The newly amended and newly entered claims are directed to peptides having SEQ ID NOs 1-21 and 30.

b. The word "composition" is definite.

As used herein, the term "composition" is not limited to covalently or non-covalently associated components. For example, the specification specifically provides at p. 16, lines 7-11 and lines 23-31 that the peptides may be covalently linked to helper peptides and lipid moieties. The specification also provides at page 17, lines 22-23 that "fusion proteins which comprise one or more peptide sequences of the invention can be used to present the appropriate T cell epitope." The specification further provides at page 21, line 29 that the composition may comprise "one or more peptides of the invention". Accordingly, withdrawal of this rejection is requested.

2. The rejections under 35 U.S.C. § 112, first paragraph are inconsistent with applicable standards or are moot.

a. The claim breadth rejections are moot.

In the pending Office Action the claims were rejected based on the number of peptides covered by the claims ("The specification does not provide adequate evidence of which of over 1,280,000,000 peptides would be capable of binding to more than one HLA molecule"). This rejection is rendered moot by the newly entered amendments and claims.

b. The pending claims are enabled.

Previously pending claims 1-3 were rejected on the basis that:

- the peptides may be inactivated before producing an effect

- the peptides may not reach the target area
- the peptides may have adverse side effects.

Although the claims are amended herein, the Examiner indicated in the Office Action that this rejection also applied to individually claimed peptides.

The Applicants respectfully traverse the basis of the rejection. The asserted rationale for the rejection does not comport with the proper standard for asserting enablement. Applicants submit that the proper standard for evaluating enablement is whether, in view of the specification and art teachings, a person of ordinary skill is enabled to make and use the claimed invention.

Published studies report that peptide therapy works. In Vitiello *et al.*, *J. Clin. Invest.* 95: 341-349 (1995) healthy HLA-A2.1-positive human subjects were induced to develop a CTL response by injection with an immunogenic peptide that was coupled to a lipid and a helper peptide. CTLs isolated from these individuals lysed HBcAg-transfected cells. Furthermore, example 14 (page 95) and Table 28 of related U.S. application No.08/205,713 (incorporated by reference into the specification) describe experiments in which transgenic mice which express human HLA-A2.1 molecules were injected in the base of the tail with 50 μg/mouse of peptides together with 140 μg/mouse of helper peptide (HBV core 128-140 (TPPAYRPPNAPIL). Using this model, peptides were tested for the ability to induce CTL response *in vivo* in transgenic mice which express human MHC molecules. As shown in Table 28, the peptides were able to induce specific CTL responses as measured by standard *in vitro* CTL assays described in Example 10.

The above-described evidence and articles show that a CTL response to specific peptides could be induced in mice and men. Thus, these peptides were unquestionably not inactivated and they reached their targets. The results reported in the above described publications and experiments further demonstrate that peptide administration is beneficial.

Further, the Examiner's concern that there may be side effects is not even justified under a 35 U.S.C. 101 rejection because of the well established general policy that undesirable secondary effects, if they exist, do not negate patentability.[1]

3. The Rejections under 35 U.S.C. § 102(b) are moot with regard to the pending claims.

The claims are amended without prejudice to further prosecution of claims of that original scope. Former Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Bosisio *et al.*, *Gazz. Chim. Ital.* 97(12)1848-57 (1967) or Fujii *et al.*, *Chem. Pharm. Bull.* 31(12)4259-4262 (1983). Bosisio *et al.*, see abstract, teach the peptide DPNKFIGLM. Fujii *et al.*, page 4261 (middle of page) teach the KPDQFVGLM peptide. In light of the claim amendments, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at

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[1] The PTO stated in the recently promulgated "Guidelines for Examination of Applications for Compliance with the Utility Requirement" that:

> E. Safety and Efficacy Considerations
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> The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the Government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs.
> ... Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness.
>
> ...Office personnel should not construe § 101, under the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans.

Thus, according to controlling PTO guidelines, even if there are significant side effects, the invention is not for this reason unpatentable.

an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 576-0200.

Respectfully submitted,

Hector A. Alicea, Ph.D.
Reg. No. 40,891

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834

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